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October 27, 1992



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Document Processing Center (TS-790)  
Office of Toxic Substances  
US Environmental Protection Agency  
401 M Street, SW  
Washington, DC 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance Audit Program

CAP ID No.: 8ECAP - 0004

Dear Sir/Madam:

On behalf of Rhône-Poulenc Inc. (RPI, CN 5266, Princeton, NJ 08543-5266) and its subsidiary Rhône-Poulenc Ag Company (RPAC), the attached study report is being submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program and the Agreement for a TSCA Section 8(e) Compliance Audit Program (CAP Agreement) executed by RPI and EPA.

The enclosed study report provides information on RPA 90946. The CAS number and name for this chemical are

. This chemical has been synthesized for research and development purposes only.

RPAC claims the CAS number and the specific chemical identity of the substance at issue to be confidential business information (CBI). The chemical substance may be nonconfidentially identified as an "anilate". The title of the enclosed report is "Acute Oral Toxicity Study of RPA 90946 in Rats". The following is a summary of the adverse effects observed in this study.

This study is being submitted under Section 8(e) because of the clinical signs observed. Ataxia, forelimb paralysis, and decreased activity were observed in animals surviving to study termination as well as those dying during the study. The oral LD<sub>50</sub> was determined to be 315 mg/kg in males rats and 208 mg/kg in female rats.

Previous TSCA Section 8(e) notices were submitted on the subject chemical on September 14, 1989 (EPA Document Control Number 8EHQ-0989-0825 S), July 1, 1991 (EPA Document Control Number 8EHQ-0791-1282 S), June 22, 1992, and October 7, 1992. RPAC has not yet received EPA Document Control Numbers for the most recent two 8(e) submissions. Several Section 8(e) notices will be submitted on this compound under the CAP.

MM  
10/8/95

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Six copies of the report and letter are provided. Three copies are stamped "Confidential Business Information" and have all confidential information underlined or circled. The other three copies are stamped "Public Notice Copy" and have all confidential information deleted.

**SUPPORT INFORMATION OF CONFIDENTIALITY CLAIMS**

1. Claims of confidentiality are being made on behalf of RPAC.
2. RPAC asserts this claim of confidentiality until such time as the chemical is approved for use in the United States. In the event that this chemical is never approved, RPAC asserts that the CBI information should be provided permanent protection. The structure and use of this chemical are unique. Disclosure of this information would provide our competitors with information on facets of our business that would be detrimental to our competitive position.
3. The information claimed as confidential has not been previously disclosed to any other governmental agency or to EPA.
4. This information has been disclosed to only a very limited number of investigators outside of RPAC who have performed either toxicity or efficacy testing. These individuals operate under a strict secrecy agreement. Any individuals who may work with this chemical will have all health/toxicology information disclosed to them as well, but only on the basis of strict secrecy and respect for the CBI nature of the information.
5. Any individual to whom the CBI is revealed are warned of the nature of the information. Further, they are informed of their obligations to maintain secrecy should they terminate their employment with RPAC.
6. None of the information claimed as confidential appears in or is referred to in any advertising or promotional materials for the chemical or the end product containing it, professional or trade publications, or any other media available to the public or to our competitors. Appropriate warnings do appear on safety data sheets, as RPAC considers that individuals who are requested to work with this chemical have every right to know as much about the chemical's toxicity as possible. Further, the information is only considered to be CBI with respect to the general public, insofar as our competitors could use the information in an unfairly competitive nature.
7. No previous confidentiality determinations have been made by EPA, other Federal agencies or courts in connection with this information.
8. RPAC believes that disclosure of this information to the general public would be likely to result in substantial harm to its competitive position. Disclosure of the **chemical name** would provide some competitors with information about the specific chemistry of this area of our research and our business. Further, the type of toxicological testing being reported in the TSCA 8(e) notice would provide competitive information about this chemical's status in the research and development process and, therefore, the time remaining until commercialization.
9. A patent has not been issued for this specific chemical structure. However, the generic chemical structure is covered by a patent that is currently pending.
10. This chemical is not available commercially. It is in an early stage of research and development for pesticide use but may be developed into a commercial product within the next 10 years.

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11. We believe that disclosure of the chemical name would allow a competitor to synthesize this chemical. RPAC has invested a large amount of time and money into research of this particular chemical family, and information on specific chemical structures would harm our competitive position.

12. Disclosure of the chemical structure might reveal information on processes used to synthesize and manufacture this compound.

13. The CAS number for this chemical is provided in the first page of the letter. This number is claimed as confidential as it provides access to the chemical name.

14. Currently, this chemical is not the subject of FIFRA regulation or reporting.

15. RPAC is not claiming "health and safety data" as CBI. Rather, we are claiming the exact chemical name as CBI.

Further questions regarding this submission may be directed to the undersigned at 919-549-2222.

Sincerely yours,



Glenn S. Simon, PhD, DABT  
Director of Toxicology

**Springborn Laboratories, Inc.****Mammalian Toxicology Division**

553 North Broadway • Spencerville, Ohio 45887 • (419) 647-4196 • Telex 4436041 • Facsimile 419-647-6560

**ACUTE ORAL TOXICITY STUDY OF  
RPA 90946 IN RATS  
(EPA-FIFRA/OECD)****PUBLIC NOTICE COPY****FINAL REPORT**Data Requirement**Guideline 81-1**Study Director**Rusty E. Rush, B.A.**Study Completed on**August 23, 1989**Performing Laboratory

**Springborn Life Sciences, Inc. (SLS)  
Toxicology and Human Safety Division  
553 North Broadway  
Spencerville, Ohio 45887**

SLS Study No.**3147.45**Submitted To

**Rhone-Poulenc Ag Company  
2TW Alexander Drive  
P. O. Box 12014  
Research Triangle Park, NC 27709**

**Page 1 of 58**
 **Springborn**  
Laboratories

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**STATEMENT OF NO DATA CONFIDENTIALITY CLAIM**

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA S10(d) (1)(A), (B), or (C).

Company: Rhone-Poulenc Ag Company

Company Agent: \_\_\_\_\_ Date: \_\_\_\_\_

Title \_\_\_\_\_ Signature \_\_\_\_\_

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**COMPLIANCE STATEMENT**

This study was conducted in compliance with the Good Laboratory Practice regulations as described by the FDA (21 CFR Part 58), the EPA (40 CFR Parts 160 and 792), and SLS's Standard Operating Procedures.

Jeffrey M. Charles, Ph.D., DABT  
Sponsor's Representative  
Rhone-Poulenc Ag Company

Date \_\_\_\_\_

Rusty E. Rush  
Rusty E. Rush, B.A.  
Study Director/Author  
Springborn Life Sciences, Inc.

Date 5-23-89

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### **QUALITY ASSURANCE STATEMENT**

This study was inspected by the Quality Assurance Unit and reports were submitted to management and the study director in accordance with SLS's Standard Operating Procedures as follows:

| <u>Phase</u>                                | <u>Date</u>      |
|---|------------------|
| Clinical Observations                       | 5/25/89          |
| Data Audit                                  | 6/22/89          |
| Draft Report Review                         | 6/26/89          |
| Final Report Review                         | 8/23/89          |
| Reports to Study Director<br>and Management | 6/26/89, 8/23/89 |

This study was conducted in compliance with the Good Laboratory Practice regulations as described by the FDA (21 CFR Part 58), the EPA (40 CFR Parts 160 and 792), and SLS's Standard Operating Procedures.

*Anita M. Bosau*  
Anita M. Bosau, Director  
Quality Assurance Unit

Date 8/23/89

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## SUMMARY

The acute oral toxicity of RPA 90946 was evaluated in rats. The study was initiated with a range-finding test using dose levels ranging from 100 to 1000 mg/kg body weight. Following the range-finding test, a full LD50 study was performed in which three groups of male and female rats were orally administered the test substance at graded dosage levels. Following dosing, the rats were observed daily and weighed weekly. A gross necropsy examination was performed on all animals at the time of death or sacrifice (day 15).

Mortality occurred as follows:

| Level<br>(mg/kg) | Incidence of Mortality |         |
|------------------|------------------------|---------|
|                  | Males                  | Females |
| 150              | -                      | 0/5     |
| 200              | -                      | 1/5     |
| 250              | 0/5                    | 5/5     |
| 300              | 2/5                    | -       |
| 350              | 4/5                    | -       |

A variety of adverse clinical signs were noted in the LD50 study animals with the most severe findings generally observed within the first three days postdose. Body weight loss was noted in one surviving female of the 200 mg/kg dose group during the day 8-15 interval. Body weight gains were exhibited by all other surviving animals during the study. The most notable necropsy observations occurred in the animals that died. These changes consisted of dark red foci on the stomach, mottled lungs, hemorrhagic thymus and congested meningeal vessels of the brain.

Under the conditions of this test, the acute oral LD50 of RPA 90946 for male rats was calculated to be 315 mg/kg with a 95% confidence interval of 285-347. In female rats, the acute oral LD50 was calculated to be 208 mg/kg with a 95% confidence interval of 196-220 mg/kg.

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## PURPOSE

To assess the acute toxicity of RPA 90946 when administered by a single oral dose to rats.

## MATERIALS AND METHODS

### In-life Phase

5/04/89 - 6/02/89

### Protocol

Test guidelines for performing this study are described in the study protocol (see Appendix I).

### Test Article

|                       |                          |
|-----------------------|--------------------------|
| Sponsor I.D.:         | RPA 90946                |
| Lot No.:              | 36-EAR-57                |
| Springborn I.D.:      | S89.007.3147A            |
| Receipt Date:         | June 6, 1989             |
| Physical Description: | White crystalline powder |
| Storage Conditions:   | Room temperature         |

The test article was prepared for dosing as a suspension in corn oil.

The Sponsor was responsible for any necessary evaluations related to chemical composition, purity, strength, stability, and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105. A Certificate of Analysis is presented, as provided by the Sponsor, in Appendix II.

### Animals and Animal Husbandry

Animal housing and care conformed to AAALAC standards and to those published in the Guide for the Care and Use of Laboratory Animals, NIH Publication No. 86-23.

Male and female young adult Sprague Dawley rats, obtained from Charles River Laboratories, Inc., were used. The animals were individually housed in suspended stainless steel cages in an environment-controlled room with a 12-hour light/dark cycle. Agway Prolab Rodent Feed and fresh water were provided to each animal ad libitum. The rats were individually identified using metal ear tags and cage cards. All animals were allowed to acclimate to the laboratory environment for a minimum of four days prior to dosing.

On several occasions, the animal room relative humidity was above the range specified in the protocol. These occurrences are considered to have had no impact on the outcome of this study.

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## Experimental Procedures

Range-Finding Study: Male and female rats were fasted overnight and then administered the test article by a single oral dose at the following levels:

| Group | Treatment Level<br>(mg/kg) | Concentration<br>(mg/ml) | Dose Volume<br>(ml/kg) | No. of Animals |         |
|-------|----------------------------|--------------------------|------------------------|----------------|---------|
|       |                            |                          |                        | Males          | Females |
| 1     | 100                        | 20                       | 5                      | 1              | 1       |
| 2     | 200                        | 40                       | 5                      | 1              | 1       |
| 3     | 300                        | 60                       | 5                      | 1              | 1       |
| 4     | 500                        | 100                      | 5                      | 1              | 1       |
| 5     | 1000                       | 200                      | 5                      | 1              | 1       |

Following dosing, the animals were observed for mortality for seven consecutive days. Results of the dose range-finding study are presented in Appendix III.

LD50 Study: The test article was administered to groups of five male and five female rats by a single oral dose at the following graded dosage levels:

| Group | Treatment Level<br>(mg/kg) | Concentration<br>(mg/ml) | Dose Volume<br>(ml/kg) | No. of Animals |         |
|-------|----------------------------|--------------------------|------------------------|----------------|---------|
|       |                            |                          |                        | Males          | Females |
| 1     | 150                        | 30                       | 5                      | -              | 5       |
| 2     | 200                        | 40                       | 5                      | -              | 5       |
| 3     | 250                        | 50                       | 5                      | 5              | 5       |
| 4     | 300                        | 60                       | 5                      | 5              | -       |
| 5     | 350                        | 70                       | 5                      | 5              | -       |

All animals were fasted overnight prior to dose administration. The animals were observed frequently on the day of dosing and once daily thereafter for the duration of the study (day 15). Mortality checks were performed twice daily. Individual body weights were determined and recorded on days 1, 8 and 15, or at death. All animals were subjected to a gross necropsy examination at the time of sacrifice (CO<sub>2</sub> asphyxiation) or death.

LD50 Calculations: LD50 values and 95% confidence intervals were calculated separately for males and females using the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Ther., 96:99-113, 1949).

## RESULTS

Mortality, clinical observations, body weight and necropsy data are summarized for LD50 study animals in Tables 1-4. Individual data for LD50 study animals are presented in Appendices IV - VI. Findings are discussed below.

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## Mortality

All deaths in the LD50 animals occurred by study day 3.

## Clinical Observations

A variety of adverse clinical signs were observed with the most severe findings generally observed within the first three days postdose. The most notable clinical signs included apparent forelimb paralysis, decreased activity, ataxia, labored breathing, urine stains and dark material on facial area.

## Body Weights

Body weight loss was noted in one 200 mg/kg surviving female during the day 8-15 interval. Body weight gains were noted in all other surviving animals during the study.

## Gross Necropsy

No remarkable gross internal findings were noted in animals which survived. In animals which died, the most notable findings consisted of dark red foci on the stomach, mottled lungs, hemorrhagic thymus and congested meningeal vessels of the brain.

## LD50 Calculations

Individual LD50 computations are given in Appendix VII.

| Sex     | Calculated LD50 Value | 95% Confidence Interval | Slope |
|---------|-----------------------|-------------------------|-------|
| Males   | 315                   | 285-347                 | 1.12  |
| Females | 208                   | 196-220                 | 1.05  |

## CONCLUSION

Under the conditions of this test, the acute oral LD50 of RPA 90946 for male rats was calculated to be 315 mg/kg with a 95% confidence interval of 285-347. In female rats, the acute oral LD50 was calculated to be 208 mg/kg with a 95% confidence interval of 196-220 mg/kg.

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Rusty E. Rush, B.A.  
Rusty E. Rush,  
Study Director

Date 8-23-84

Reviewed by:

Patricia K. Jenkins, L.A.T.  
Supervisor, Acute Toxicology

Date 8-23-84

Joseph C. Siglin  
Joseph C. Siglin, B.A.  
Toxicologist

Date 8/23/84

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TABLE 1  
ACUTE ORAL TOXICITY STUDY IN RATS  
MORTALITY SUMMARY--LD50 STUDY

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 CLIENT: RHONE-POULENC AG COMPANY

**TABLE 2**  
**ACUTE ORAL TOXICITY STUDY IN RATS**  
**SUMMARY OF CLINICAL OBSERVATIONS--LD50 STUDY**  
**(TOTAL INCIDENCE/NO. OF ANIMALS)**

|                                     |                              | <b>MALE</b>      |                 |           |           |      |  |
|-------------------------------------|------------------------------|------------------|-----------------|-----------|-----------|------|--|
|                                     |                              | TABLE RANGE:     | DAY 1 TO DAY 15 |           |           |      |  |
|                                     |                              | GROUP:<br>LEVEL: | 250 MG/KG       | 300 MG/KG | 350 MG/KG |      |  |
| NORMAL                              | -NO CLINICAL SIGNS           |                  | 73/ 5           | 44/ 5     | 19/ 4     |      |  |
| DEAD                                | -FOUND DEAD                  |                  | 0/ 0            | 2/ 2      | 4/ 4      |      |  |
| ACTIVITY                            |                              |                  | 6/ 4            | 13/ 5     | 13/ 5     |      |  |
| -ATAxia                             |                              |                  | 3/ 3            | 5/ 4      | 5/ 5      |      |  |
| -APPARENT PARALYSIS-FRONT FORELIMBS |                              |                  | 1/ 1            | 0/ 0      | 0/ 0      |      |  |
| -SALIVATION                         |                              |                  | 5/ 4            | 4/ 4      | 7/ 5      |      |  |
| -ACTIVITY DECREASED                 |                              |                  | 0/ 0            | 0/ 0      | 2/ 2      |      |  |
| -LABORED BREATHING                  |                              |                  |                 |           |           |      |  |
| BODY                                | -URINE STAIN                 |                  | 0/ 0            | 2/ 2      | 2/ 2      |      |  |
| HAIRLOSS                            |                              |                  |                 |           |           | 0/ 0 |  |
| -LEFT FORELIMB                      |                              |                  | 5/ 1            | 0/ 0      | 0/ 0      |      |  |
| -RIGHT FORELIMB                     |                              |                  | 5/ 1            | 0/ 0      | 0/ 0      |      |  |
| -RIGHT HIP                          |                              |                  | 1/ 1            | 0/ 0      | 0/ 0      |      |  |
| EYES                                | -DARK MATERIAL AROUND EYE(S) |                  | 0/ 0            | 1/ 1      | 0/ 0      |      |  |

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TABLE 2  
ACUTE ORAL TOXICITY STUDY IN RATS  
SUMMARY OF CLINICAL OBSERVATIONS—LD<sub>50</sub> STUDY  
(TOTAL INCIDENCE/NO. OF ANIMALS)

— M A L E —

| TABLE RANGE:                | DAY 1     | TO DAY 15 |           |
|-----------------------------|-----------|-----------|-----------|
| GROUP:                      | 1         | 2         | 3         |
| LEVEL:                      | 250 MG/KG | 300 MG/KG | 350 MG/KG |
| NOSE/MOUTH                  | 2/ 2      | 3/ 2      | 5/ 4      |
| -DARK MATERIAL AROUND NOSE  | 0/ 0      | 0/ 0      | 1/ 1      |
| -DARK MATERIAL AROUND MOUTH |           |           |           |

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TABLE 2  
ACUTE ORAL TOXICITY STUDY IN RATS  
SUMMARY OF CLINICAL OBSERVATIONS—LD<sub>50</sub> STUDY  
(TOTAL INCIDENCE/NO. OF ANIMALS)

|                                     |                              | F E M A L E      |                 |           |   |           |  |
|-------------------------------------|------------------------------|------------------|-----------------|-----------|---|-----------|--|
|                                     |                              | TABLE RANGE:     | DAY 1 TO DAY 15 | 2         | 3 | 250 MG/KG |  |
|                                     |                              | GROUP:<br>LEVEL: | 150 MG/KG       | 200 MG/KG |   |           |  |
| NORMAL                              | -NO CLINICAL SIGNS           |                  | 1/ 5            | 50/ 5     |   | 15/ 5     |  |
| DEAD                                | -FOUND DEAD                  |                  | 0/ 0            | 1/ 1      |   | 5/ 5      |  |
| ACTIVITY                            |                              |                  | 4/ 4            | 18/ 5     |   | 5/ 5      |  |
| -ATAXIA                             |                              |                  | 3/ 3            | 8/ 5      |   | 5/ 5      |  |
| -APPARENT PARALYSIS-FRONT FORELIMBS |                              |                  | 3/ 3            | 9/ 5      |   | 5/ 5      |  |
| -ACTIVITY DECREASED                 |                              |                  |                 |           |   |           |  |
| EXCRETA/EMESIS                      |                              |                  | 0/ 0            | 2/ 1      |   | 0/ 0      |  |
| -FEW FECES                          |                              |                  |                 |           |   |           |  |
| BODY                                |                              |                  | 0/ 0            | 6/ 2      |   | 1/ 1      |  |
| -URINE STAIN                        |                              |                  | 0/ 0            | 3/ 1      |   | 0/ 0      |  |
| -ROUGH COAT                         |                              |                  |                 |           |   |           |  |
| EYES                                | -DARK MATERIAL AROUND EYE(S) |                  | 0/ 0            | 2/ 2      |   | 0/ 0      |  |
| NOSE/MOUTH                          | -DARK MATERIAL AROUND NOSE   |                  | 0/ 0            | 5/ 4      |   | 1/ 1      |  |

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TABLE 3  
 ACUTE ORAL TOXICITY STUDY IN RATS  
 SUMMARY OF BODY WEIGHT DATA (GRAMS)—LD50 STUDY

| DAY | MEAN | S.D. | N | MALE |      |   | 350 MG/KG |
|-----|------|------|---|------|------|---|-----------|
|     |      |      |   | 1    | 2    | 3 |           |
| 1   | 207  | 7.2  | 5 | 260  | 16.5 | 5 | 236       |
| 8   | 284  | 8.9  | 5 | 324  | 9.5  | 3 | 326       |
| 15  | 338  | 14.1 | 5 | 371  | 14.0 | 3 | 392       |

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TABLE 3  
ACUTE ORAL TOXICITY STUDY IN RATS  
SUMMARY OF BODY WEIGHT DATA (GRAMS)—LD50 STUDY

| DAY | GROUP:<br>LEVEL:  | F E M A L E      |                  |                 |
|-----|-------------------|------------------|------------------|-----------------|
|     |                   | 1<br>150 MG/KG   | 2<br>200 MG/KG   | 3<br>250 MG/KG  |
| 1   | MEAN<br>S.D.<br>N | 199<br>9.0<br>5  | 210<br>8.5<br>5  | 194<br>6.5<br>5 |
| 8   | MEAN<br>S.D.<br>N | 226<br>15.0<br>5 | 226<br>5.3<br>4  | 0<br>0.0<br>0   |
| 15  | MEAN<br>S.D.<br>N | 242<br>16.9<br>5 | 235<br>14.2<br>4 | 0<br>0.0<br>0   |

SLS STUDY NO.: 3147 45  
 CLIENT: RHONE-POULENC AG COMPANY

TABLE 4  
 ACUTE ORAL TOXICITY STUDY IN RATS  
 SUMMARY OF GROSS NECROPSY OBSERVATIONS—LD50 STUDY  
 (FOUND DEAD)

| NUMBER OF ANIMALS IN DOSE GROUP<br>NUMBER OF ANIMALS FOUND DEAD   | LEVEL (MG/KG): | MALE                  |                   |                   | FEMALE      |             |                   |
|---|----------------|-----------------------|-------------------|-------------------|-------------|-------------|-------------------|
|   |                | GROUP:<br>1<br>2<br>3 | 250<br>300<br>350 | 150<br>200<br>250 | 1<br>2<br>3 | 1<br>2<br>3 | 150<br>200<br>250 |
|   |                | 5<br>0<br>2           | 5<br>2<br>4       | 5<br>0<br>2       | 5<br>0<br>1 | 5<br>0<br>1 | 5<br>0<br>1       |
| SMALL INTESTINE<br>-DARK GREEN MUCOID CONTENTS  |                | 0                     | 1                 | 2                 | 0           | 0           | 2                 |
| BRAIN<br>-MENINGEAL VESSELS - CONGESTED   |                | 0                     | 2                 | 3                 | 0           | 0           | 0                 |
| LUNGS<br>-MOTTLED   |                | 0                     | 0                 | 3                 | 0           | 0           | 0                 |
| STOMACH<br>-DARK RED FOCI<br>-DARK BROWN MUCOID CONTENTS<br>-REDDISH-BROWN FLUID CONTENTS   |                | 0                     | 2                 | 3                 | 0           | 1           | 5                 |
| THYMUS<br>-HEMORRHAGIC  |                | 0                     | 1                 | 2                 | 0           | 0           | 2                 |
| EXT. APPEARANCE<br>-DRYED RED MATERIAL AROUND MOUTH<br>-DRYED LIGHT RED MATTING AROUND MOUTH<br>-DRYED RED MATERIAL AROUND NOSE<br>-DRYED CLEAR MATTING AROUND MOUTH<br>-DRYED RED MATERIAL AROUND EYES<br>-URINE STAIN |                | 0                     | 0                 | 2                 | 0           | 0           | 1                 |
| NO REMARKABLE FINDINGS - ALL EXAMINED TISSUES   |                | 0                     | 0                 | 0                 | 0           | 0           | 0                 |

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

TABLE 4  
ACUTE ORAL TOXICITY STUDY IN RATS  
SUMMARY OF GROSS NECROPSY OBSERVATIONS--LD50 STUDY  
(SCHEDULED SACRIFICE)

| NUMBER OF ANIMALS IN DOSE GROUP<br>NUMBER OF ANIMALS TERMINALLY SACRIFICED | LEVEL (MG/KG): | MALE          |     |     | FEMALE |     |     |
|--|----------------|---------------|-----|-----|--------|-----|-----|
|  |                | GROUP:<br>250 | 300 | 350 | 150    | 200 | 250 |
|  |                | 5             | 5   | 5   | 5      | 5   | 5   |
|  |                | 5             | 3   | 1   | 5      | 4   | 0   |
| EXT. APPEARANCE<br>-HAIRLOSS   |                | 1             | 0   | 0   | 0      | 0   | 0   |
| NO REMARKABLE FINDINGS - ALL EXAMINED TISSUES                              |                | 4             | 3   | 1   | 5      | 4   | 0   |

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**APPENDIX I**

**PROTOCOL**

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**ACUTE ORAL TOXICITY STUDY IN RATS WITH RPA 90946  
(EPA-FIFRA/OECD)**

**Study No. 3147.45**

**Springborn Life Sciences, Inc.  
Toxicology & Human Safety Division  
553 North Broadway  
Spencerville, Ohio 45887**

**Rusty E. Rush, B.A.  
Study Director**

**For**

**Rhone-Poulenc Ag Company  
2TW Alexander Drive  
P.O. Box 12014  
Research Triangle Park, NC 27709  
(919) 549-2166**

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SLS Study No. 3147.45

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## I. PURPOSE

To assess the short-term toxicity of a test article in rats when administered by the oral route.

## II. SPONSOR

Rhone-Poulenc Ag Company  
2TW Alexander Drive  
Research Triangle Park, NC 27709

## III. SPONSOR'S REPRESENTATIVE

Jeffrey M. Charles, Ph.D., DABT  
PHONE: (919) 549-2238  
FAX: (919) 549-8525

## IV. TESTING LABORATORY

Springborn Life Sciences, Inc.  
Toxicology & Human Safety Division  
553 North Broadway  
Spencerville, OH 45887  
Phone: (419) 647-4196  
FAX: (419) 647-6560

## V. SPRINGBORN PERSONNEL RESPONSIBILITIES

- |   |  |
|---|--|
| A. Rusty E. Rush, B.A.<br>Study Director                  | G. Nik Mahmood, Ph.D.<br>Toxicologist                                  |
| B. Dean E. Rodwell, M.S.<br>Director of Research          | H. Yen-Sun Ho, Ph.D.<br>Senior Analytical Chemist                      |
| C. James T. F. Liao, DVM, Ph.D.<br>Director of Toxicology | I. John J. McKenzie, B.S.<br>Assistant Toxicologist                    |
| D. Anita M. Bosau, Director<br>Quality Assurance Unit     | J. William T. Collins, DVM, Ph.D.<br>Consultant Veterinarian           |
| E. Joseph C. Siglin, B.A.<br>Toxicologist                 | K. Robert G. Geil, DVM<br>Diplomate A.C.V.P.<br>Consultant Pathologist |
| F. Michael D. Mercieca, B.S.<br>Toxicologist              |  |

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**VI. TEST ARTICLE IDENTIFICATION**

Sponsor I.D.: RPA 90946

Springborn I.D.: S89.007.3147

**VII. TEST ARTICLE CHARACTERIZATION**

The Sponsor is responsible for any necessary evaluations related to chemical composition, purity, strength, stability and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105.

**VIII. TEST ARTICLE PREPARATION**

The test article may be administered as received or diluted with an appropriate vehicle. Selected dosages may be achieved by varying the dosage volume or by administering a constant volume with adjustment of test article concentration in the vehicle. Specific preparation procedures will be reviewed with the Sponsor prior to study initiation. The test article will be prepared and/or dispensed fresh for dose administration.

**IX. TEST SYSTEM JUSTIFICATION**

The rat is the system of choice since it has been used historically for this type of study and will allow the data to be compared to those for other compounds.

**X. ANIMALS AND ANIMAL HUSBANDRY**

A. Strain/Species: Sprague Dawley rats

B. Source: an SLS and USDA approved animal supplier

C. Number: 5 males and 5 females for limit test  
1/sex/level for LD50 range-finding test  
5/sex/level for LD50 study

D. Weight: approximately 200 to 300 g

E. Acclimation Period: minimum of 5 days

F. Animal Identification: metal ear tags

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G. Food and Water: Commercial laboratory feed and water will be provided ad libitum. No contaminants are anticipated in the feed and water which would compromise the purposes of the study. Water is analyzed for contaminants on an annual basis in accordance with SLS's Standard Operating Procedures.

H. Housing and Animal Care: One per cage in suspended stainless steel cages. 12/12 hour light/dark cycle. All housing and care conforms to AAALAC standards and to those published in the Guide for the Care and Use of Laboratory Animals, NIH Publication No. 86-23. Animal room temperature and relative humidity will be maintained at 65-78°F and 30-70%, respectively. Prior to assignment to the study, the animals will be closely examined for signs of disease and/or presence of physical or behavioral abnormalities. Only healthy animals will be used for the study.

**XI. EXPERIMENTAL DESIGN**

The Sponsor may select the following options:

- Perform a range-finding study, then perform a limit test or a full LD50 study
- Perform a limit test (5000 mg/kg)
- Perform an LD50 test (based on estimated LD50 < 5000 mg/kg, range-finding or limit test data)

**XII. EXPERIMENTAL PROCEDURES**

**A. Limit Test**

**1. Dosing**

The test article will be administered orally by gavage to a single group of five male and five female rats at a level of 5000 mg/kg body weight. The animals will be fasted overnight prior to dose administration.

**2. Body Weights**

Individual body weights will be obtained on the day of dosing (day 1) and on days 8 and 15. Any animals which die on test after day 1 will be weighed.

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### **3. Observations**

Animals will be observed for mortality and toxic effects two or three times on study day 1 (postexposure) and daily thereafter. Clinical observations will include, but not be limited to, changes in the skin and fur, eyes and mucous membranes, respiratory system, circulatory system, autonomic and central nervous systems, somatomotor activity, and behavior pattern. A mortality check will be performed twice daily, in the morning and afternoon.

### **4. Termination**

All animals which die spontaneously during the study or are killed at termination (day 15) will be necropsied. Animals will be euthanized by CO<sub>2</sub> asphyxiation.

### **B. Range-Finding Study**

The dose range-finding study will evaluate the lethal potential of the test article at graded dosage levels. One animal/sex/level will receive the test article by a single oral gavage. The rats will be fasted overnight in preparation for dose administration. The animals will be weighed individually on the day of dosing and observed for mortality for one week following dosing (days 1-8). Animals which die will be discarded without necropsy and those which survive will be euthanized by CO<sub>2</sub> asphyxiation and discarded.

### **C. LD50 Study**

1. The LD50 for the test article may be determined by administering the test article by a single oral dose at graded dosage levels to groups of five male and five female rats.
2. Experimental procedures for each group included in the LD50 study will be the same as those described in Sections XII.A.1-4.

### **XIII. STATISTICAL ANALYSIS**

The LD50 and 95% confidence interval will be calculated separately for males, females and the combined sexes (when possible) using a computer adaptation of the method of Litchfield and Wilcoxon. An acceptable alternative method may be used if necessary.

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### **XIV. REPORT**

The final report will include all information necessary to provide a complete and accurate description and evaluation of the test procedures and results. Two copies of the final report (one bound and one unbound) will be submitted to the Sponsor. The final report will be reviewed by SLS's QA section in accordance with the pertinent government regulations.

### **XV. GOOD LABORATORY PRACTICES**

This study will be performed in accordance with the principles of Good Laboratory Practice regulations as described by the FDA (21 CFR Part 58) and the EPA (40 CFR Parts 160 and 792). If, after a study is underway, it becomes necessary to make changes on the approved protocol, the revisions and reasons for change shall be documented, reported to the Sponsor and shall then become part of the permanent file for the study. Similarly the Sponsor shall be notified as soon as practical whenever an event occurs that is unexpected and may have an effect on the validity of the study.

### **XVI. DATA RETENTION**

The raw data and the final report will be on file at the testing laboratory. The Sponsor will be notified before final disposition of these items. Unused test articles will be returned to the Sponsor unless requested otherwise.

### **XVII. REGULATORY AGENCY**

This study may be submitted to the following regulatory agencies: EPA/OECD.

### **XVIII. SCHEDULE**

Proposed Starting Date: 3 May 1989

Proposed Completion Date: 28 June 1989

8-23-89, 26 8-23-89

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XIX. PROTOCOL APPROVAL

Rusty E. Rush  
Rusty E. Rush, B.A.  
Study Director (SLS)

Date 5-3-89

Jeffrey E. Charles  
Jeffrey E. Charles, Ph.D., DABT  
Sponsor's Representative

Date 5/12/89

Anita M. Bosau  
Anita M. Bosau, Director  
Quality Assurance Unit

Date 5/3/89

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**APPENDIX II**

**CERTIFICATE OF ANALYSIS**

 RHÔNE-POULENC

RHÔNE-POULENC AG COMPANY

*R. E. Rush*  
Rusty E. Rush, B.A.  
Study Director

Date 1-6-80

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CERTIFICATE OF ANALYSIS

RPA-90946

Sample IdentityReference number: 36-EAR-57  
Analy. log no.: 011522DisbursementRequested by:  
Amount disbursed:  
Disbursed to:  
Address:

Intended use:

Chemical Identity

Code name: RPA-90946

Analysis

- Physical state, appearance: white, crystalline powder
- Purity: 98.04 wt.-%
- Date of Analysis: March 7, 1989
- Analysis reference(s): Data File: 089-LJH-166  
Notebook: 25-LJH-1

Analyst G. J. Wheeler Date 4/14/89  
G. J. WheelerSpecial Hazards

Normal handling precautions should be taken to prevent the material entering the eyes, being inhaled or coming into contact with the skin, food, drink, or smoking materials.

Approval

I certify that this material was analyzed in a laboratory following Good Laboratory Practice Standards.

Authorized Signature

*L. J. Helfant*  
L.J. Helfant  
Research Scientist4/14/89  
DateNote:

The only warranty given by this certificate is that when a sample was examined on the above date the purity of the sample was assessed to be as stated above.

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**APPENDIX III**

**INDIVIDUAL RANGE-FINDING STUDY DATA**

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SLS STUDY NO: 3147 45                    ACUTE ORAL TOXICITY STUDY IN RATS  
CLIENT: RHONE-POULENC AG COMPANY        INDIVIDUAL RANGE-FINDING STUDY DATA

| SEX    | TREATMENT LEVEL (MG/KG) | ANIMAL NUMBER | DOSE (ML) | BODY WT. DAY 1 (G) | DAY OF DEATH |
|--------|-------------------------|---------------|-----------|--------------------|--------------|
| MALE   | 100                     | 7277          | 1.6       | 321                | -            |
|        | 200                     | 7162          | 1.6       | 315                | -            |
|        | 300                     | 7153          | 1.6       | 312                | 3            |
|        | 500                     | 7167          | 1.2       | 243                | 2            |
|        | 1000                    | 7174          | 1.3       | 252                | 2            |
|        |                         |               |           |                    |              |
| FEMALE | 100                     | 7134          | 1.2       | 233                | -            |
|        | 200                     | 7120          | 1.2       | 231                | -            |
|        | 300                     | 7112          | 1.1       | 226                | 3            |
|        | 500                     | 7184          | 1.1       | 217                | 2            |
|        | 1000                    | 7183          | 1.2       | 231                | 2            |
|        |                         |               |           |                    |              |

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SLS Study No. 3147.45

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**APPENDIX IV**

**INDIVIDUAL CLINICAL OBSERVATIONS  
(POSITIVE FINDINGS--LD50 STUDY)**

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL CLINICAL OBSERVATIONS  
STUDY DAYS: 1 THROUGH 15

| ANIMAL | SEX | GROUP     | CATEGORY   | STUDY DAY | GRADE OBSERVATIONS |                                    |
|--------|-----|-----------|------------|-----------|--------------------|------------------------------------|
|        |     |           |            |           | ACTIVITY           | ATAXIA                             |
| 7650   | M   | 300 MG/KG | ACTIVITY   | 1         | P                  | ATAXIA                             |
|        |     |           | ACTIVITY   | 1         | P                  | ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P                  | APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | BODY       | 3         | P                  | URINE STAIN                        |
| 7657   | M   | 300 MG/KG | ACTIVITY   | 1         | P                  | ATAXIA                             |
|        |     |           | ACTIVITY   | 1         | P                  | APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P                  | ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P                  | APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P                  | ACTIVITY DECREASED                 |
|        |     |           | DEAD       | 3         | P                  | FOUND DEAD                         |
| 7660   | M   | 300 MG/KG | ACTIVITY   | 1         | P                  | ATAXIA                             |
|        |     |           | ACTIVITY   | 1         | P                  | ATAXIA                             |
|        |     |           | ACTIVITY   | 1         | P                  | ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P                  | ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P                  | ATAXIA                             |
|        |     |           | ACTIVITY   | 3         | P                  | ATAXIA                             |
| 7663   | M   | 300 MG/KG | ACTIVITY   | 1         | P                  | ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P                  | APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P                  | ACTIVITY DECREASED                 |
|        |     |           | NOSE/MOUTH | 2         | P                  | DARK MATERIAL AROUND NOSE          |
|        |     |           | DEAD       | 3         | P                  | FOUND DEAD                         |
| 7671   | M   | 300 MG/KG | NOSE/MOUTH | 1         | P                  | DARK MATERIAL AROUND NOSE          |
|        |     |           | ACTIVITY   | 2         | P                  | ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P                  | APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P                  | ACTIVITY DECREASED                 |
|        |     |           | BODY       | 2         | P                  | URINE STAIN                        |
|        |     |           | EYES       | 2         | P                  | DARK MATERIAL AROUND EYE(S)        |

GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-SEVERE, P-PRESENT

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL CLINICAL OBSERVATIONS  
STUDY DAYS: 1 THROUGH 15

| ANIMAL | SEX | GROUP     | CATEGORY   | STUDY DAY | GRADE OBSERVATIONS                   |
|--------|-----|-----------|------------|-----------|--------------------------------------|
| 7671   | M   | 300 MG/KG | NOSE/MOUTH | 2         | P DARK MATERIAL AROUND NOSE          |
| 7653   | M   | 250 MG/KG | ACTIVITY   | 1         | P SALIVATION                         |
|        |     |           | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | HAIRLOSS   | 11        | P ACTIVITY DECREASED                 |
|        |     |           | HAIRLOSS   | 11        | P LEFT FORELIMB                      |
|        |     |           | HAIRLOSS   | 12        | P RIGHT FORELIMB                     |
|        |     |           | HAIRLOSS   | 12        | P LEFT FORELIMB                      |
|        |     |           | HAIRLOSS   | 12        | P RIGHT FORELIMB                     |
|        |     |           | HAIRLOSS   | 13        | P LEFT FORELIMB                      |
|        |     |           | HAIRLOSS   | 13        | P RIGHT FORELIMB                     |
|        |     |           | HAIRLOSS   | 14        | P LEFT FORELIMB                      |
|        |     |           | HAIRLOSS   | 14        | P RIGHT FORELIMB                     |
|        |     |           | HAIRLOSS   | 15        | P LEFT FORELIMB                      |
|        |     |           | HAIRLOSS   | 15        | P RIGHT FORELIMB                     |
|        |     |           | HAIRLOSS   | 15        | P RIGHT HIP                          |
|        |     |           | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | NOSE/MOUTH | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P DARK MATERIAL AROUND NOSE          |
|        |     |           | NOSE/MOUTH | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 3         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 3         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 3         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 3         | P ATAXIA                             |

GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-SEVERE, P-PRESENT

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL CLINICAL OBSERVATIONS  
STUDY DAYS: 1 THROUGH 15

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| ANIMAL | SEX | GROUP     | CATEGORY                              | STUDY DAY | GRADE OBSERVATIONS   |
|--------|-----|-----------|---------------------------------------|-----------|--|
| 7652   | M   | 350 MG/KG | ACTIVITY ACTIVITY NOSE/MOUTH          | 1         | P ATAXIA<br>P ATAXIA<br>P DARK MATERIAL AROUND NOSE                              |
|        |     |           | ACTIVITY ACTIVITY                     | 2         | P ATAXIA<br>P APPARENT PARALYSIS-FRONT FORELIMBS                                 |
|        |     |           | ACTIVITY                              | 2         | P ACTIVITY DECREASED   |
|        |     |           | ACTIVITY NOSE/MOUTH                   | 3         | P DARK MATERIAL AROUND NOSE  |
| 7655   | M   | 350 MG/KG | ACTIVITY ACTIVITY ACTIVITY DEAD       | 1         | P ATAXIA<br>P ATAXIA<br>P ACTIVITY DECREASED                                     |
|        |     |           | ACTIVITY ACTIVITY                     | 2         | P FOUND DEAD<br>P ATAXIA<br>P APPARENT PARALYSIS-FRONT FORELIMBS                 |
|        |     |           | ACTIVITY                              | 2         | P ACTIVITY DECREASED   |
|        |     |           | ACTIVITY BODY                         | 2         | P LABORED BREATHING<br>P URINE STAIN   |
|        |     |           | NOSE/MOUTH                            | 2         | P DARK MATERIAL AROUND NOSE  |
| 7658   | M   | 350 MG/KG | ACTIVITY ACTIVITY ACTIVITY DEAD       | 2         | P DARK MATERIAL AROUND MOUTH<br>P ATAXIA<br>P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY                              | 2         | P ACTIVITY DECREASED   |
|        |     |           | ACTIVITY                              | 3         | P FOUND DEAD   |
| 7659   | M   | 350 MG/KG | ACTIVITY ACTIVITY ACTIVITY NOSE/MOUTH | 1         | P ATAXIA<br>P APPARENT PARALYSIS-FRONT FORELIMBS                                 |
|        |     |           | ACTIVITY                              | 2         | P ACTIVITY DECREASED   |
|        |     |           | ACTIVITY                              | 2         | P DARK MATERIAL AROUND NOSE  |
|        |     |           | DEAD                                  | 3         | P FOUND DEAD<br>P ATAXIA   |
| 7667   | M   | 350 MG/KG | ACTIVITY                              | 1         | P ATAXIA   |

GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-SEVERE, P-PRESENT

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

**ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL CLINICAL OBSERVATIONS  
STUDY DAYS: 1 THROUGH 15**

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| ANIMAL | SEX | GROUP     | CATEGORY   | STUDY DAY | GRADE OBSERVATIONS                   |
|--------|-----|-----------|------------|-----------|--------------------------------------|
| 7667   | M   | 350 MG/KG | ACTIVITY   | 1         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 1         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 1         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P LABORED BREATHING                  |
|        |     |           | BODY       | 2         | P URINE STAIN                        |
|        |     |           | NOSE/MOUTH | 2         | P DARK MATERIAL AROUND NOSE          |
|        |     |           | DEAD       | 3         | P FOUND DEAD                         |
| 7682   | F   | 150 MG/KG | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
| 7686   | F   | 150 MG/KG | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
| 7687   | F   | 150 MG/KG | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | DEAD       | 3         | P FOUND DEAD                         |
|        |     |           | ACTIVITY   | 2         | P ATAXIA                             |
| 7695   | F   | 150 MG/KG | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
| 7672   | F   | 250 MG/KG | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P FOUND DEAD                         |
|        |     |           | DEAD       | 3         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P FOUND DEAD                         |
|        |     |           | DEAD       | 3         | P ATAXIA                             |
| 7677   | F   | 250 MG/KG | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 2         | P FOUND DEAD                         |
|        |     |           | ACTIVITY   | 2         | P ATAXIA                             |
| 7679   | F   | 250 MG/KG | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |

GRADE CODE: 1-SLIGHT; 2-MODERATE; 3-SEVERE, P-PRESENT

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL CLINICAL OBSERVATIONS  
STUDY DAYS: 1 THROUGH 15

| ANIMAL | SEX | GROUP     | CATEGORY   | STUDY DAY | GRADE OBSERVATIONS                   |
|--------|-----|-----------|------------|-----------|--------------------------------------|
| 7679   | F   | 250 MG/KG | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | DEAD       | 3         | P FOUND DEAD                         |
| 7681   | F   | 250 MG/KG | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | BODY       | 2         | P URINE STAIN                        |
|        |     |           | DEAD       | 3         | P FOUND DEAD                         |
| 7690   | F   | 250 MG/KG | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | NOSE/MOUTH | 2         | P DARK MATERIAL AROUND NOSE          |
|        |     |           | DEAD       | 3         | P FOUND DEAD                         |
| 7674   | F   | 200 MG/KG | ACTIVITY   | 1         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 1         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY   | 3         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 3         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY   | 3         | P ACTIVITY DECREASED                 |
|        |     |           | BODY       | 3         | P URINE STAIN                        |
|        |     |           | EYES       | 3         | P DARK MATERIAL AROUND EYE(S)        |
|        |     |           | NOSE/MOUTH | 3         | P DARK MATERIAL AROUND NOSE          |
|        |     |           | ACTIVITY   | 4         | P ATAXIA                             |
|        |     |           | BODY       | 4         | P URINE STAIN                        |
|        |     |           | ACTIVITY   | 5         | P ATAXIA                             |
|        |     |           | BODY       | 5         | P URINE STAIN                        |
| 7676   | F   | 200 MG/KG | ACTIVITY   | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY   | 2         | P ACTIVITY DECREASED                 |

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL CLINICAL OBSERVATIONS  
STUDY DAYS: 1 THROUGH 15

| ANIMAL | SEX | GROUP     | CATEGORY       | STUDY DAY | GRADE OBSERVATIONS                   |
|--------|-----|-----------|----------------|-----------|--------------------------------------|
| 7676   | F   | 200 MG/KG | ACTIVITY       | 3         | P ATAXIA                             |
|        |     |           | ACTIVITY       | 3         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY       | 3         | P ACTIVITY DECREASED                 |
|        |     |           | EYES           | 3         | P DARK MATERIAL AROUND EYE(S)        |
|        |     |           | NOSE/MOUTH     | 3         | P DARK MATERIAL AROUND NOSE          |
|        |     |           | ACTIVITY       | 4         | P ATAXIA                             |
|        |     |           | ACTIVITY       | 2         | P ATAXIA                             |
|        |     |           | ACTIVITY       | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY       | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY       | 3         | P ATAXIA                             |
|        |     |           | ACTIVITY       | 3         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY       | 1         | P ATAXIA                             |
|        |     |           | ACTIVITY       | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY       | 2         | P ACTIVITY DECREASED                 |
|        |     |           | ACTIVITY       | 2         | P DARK MATERIAL AROUND NOSE          |
|        |     |           | NOSE/MOUTH     | 2         | P FOUND DEAD                         |
|        |     |           | DEAD           | 3         | P ATAXIA                             |
|        |     |           | ACTIVITY       | 1         | P ATAXIA                             |
|        |     |           | ACTIVITY       | 1         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY       | 1         | P ATAXIA                             |
|        |     |           | ACTIVITY       | 2         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY       | 2         | P ACTIVITY DECREASED                 |
|        |     |           | EXCRETA/EMESIS | 2         | P FEW FECES                          |
|        |     |           | NOSE/MOUTH     | 2         | P DARK MATERIAL AROUND NOSE          |
|        |     |           | ACTIVITY       | 3         | P ATAXIA                             |
|        |     |           | ACTIVITY       | 3         | P APPARENT PARALYSIS-FRONT FORELIMBS |
|        |     |           | ACTIVITY       | 3         | P ACTIVITY DECREASED                 |
|        |     |           | EXCRETA/EMESIS | 3         | P FEW FECES                          |

GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-SEVERE, P-PRESENT

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL CLINICAL OBSERVATIONS  
STUDY DAYS: 1 THROUGH 15

| ANIMAL SEX | GROUP     | CATEGORY        | STUDY DAY | GRADE OBSERVATIONS                           |
|------------|-----------|-----------------|-----------|--|
| 7693 F     | 200 MG/KG | BODY NOSE/MOUTH | 3         | P URINE STAIN<br>P DARK MATERIAL AROUND NOSE |
|            |           | ACTIVITY        | 4         | P ATAXIA                                     |
|            |           | ACTIVITY        | 4         | P APPARENT PARALYSIS-FRONT FORELIMBS         |
|            |           | BODY            | 4         | P URINE STAIN                                |
|            |           | BODY            | 5         | P URINE STAIN                                |
|            |           | BODY            | 6         | P ROUGH COAT                                 |
|            |           | BODY            | 7         | P ROUGH COAT                                 |
|            |           | BODY            | 8         | P ROUGH COAT                                 |

GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-SEVERE, P-PRESENT

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SLS Study No. 3147.45

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**APPENDIX V**

**INDIVIDUAL BODY WEIGHT DATA  
(LD50 STUDY)**

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL BODY WEIGHT DATA (GRAMS)

MALE GROUP: 250 MG/KG

| DAY    | 1   | 8   | 15   |
|--------|-----|-----|------|
| ANIMAL |     |     |      |
| 7649   | 197 | 277 | 324  |
| 7653   | 211 | 283 | 340  |
| 7661   | 216 | 298 | 354  |
| 7666   | 204 | 276 | 324  |
| 7669   | 209 | 286 | 350  |
| MEAN   | 207 | 284 | 338  |
| S.D.   | 7.2 | 8.9 | 14.1 |
| N      | 5   | 5   | 5    |

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SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL BODY WEIGHT DATA (GRAMS)

MALE GROUP: 300 MG/KG

| DAY           | 1    | 8    | 15   |
|---------------|------|------|------|
| <b>ANIMAL</b> |      |      |      |
|               | 7650 | 254  | 313  |
|               | 7657 | 268  | 360  |
|               | 7660 | 265  | 327  |
|               | 7663 | 234  | 387  |
|               | 7671 | 277  | 331  |
|               |      |      | 367  |
|               |      |      | 324  |
|               |      | 260  | 371  |
|               |      | 16.5 | 14.0 |
|               |      | 5    | 3    |
| <b>MEAN</b>   |      |      |      |
|               |      | S.D. |      |
|               |      | N    |      |

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL BODY WEIGHT DATA (GRAMS)

MALE GROUP: 350 MG/KG

| DAY    | 1    | 8   | 15  |
|--------|------|-----|-----|
| ANIMAL |      |     |     |
| 7652   | 252  | 326 | 392 |
| 7655   | 230  |     |     |
| 7658   | 221  |     |     |
| 7659   | 235  |     |     |
| 7667   | 240  |     |     |
| MEAN   | 236  | 326 | 392 |
| S.D.   | 11.5 | 0.0 | 0.0 |
| N      | 5    | 1   | 1   |

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL BODY WEIGHT DATA (GRAMS)

FEMALE GROUP: 150 MG/KG

| DAY    | 1   | 8    | 15   |
|--------|-----|------|------|
| ANIMAL |     |      |      |
| 7675   | 207 | 237  | 254  |
| 7682   | 194 | 221  | 234  |
| 7686   | 186 | 202  | 219  |
| 7687   | 207 | 239  | 262  |
| 7695   | 201 | 229  | 242  |
| MEAN   | 199 | 226  | 242  |
| S.D.   | 9.0 | 15.0 | 16.9 |
| N      | 5   | 5    | 5    |

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SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL BODY WEIGHT DATA (GRAMS)

FEMALE GROUP: 200 MG/KG

| DAY    | 1   | 8   | 15   |
|--------|-----|-----|------|
| ANIMAL |     |     |      |
| 7674   | 208 | 221 | 217  |
| 7676   | 206 | 223 | 246  |
| 7678   | 199 | 226 | 231  |
| 7683   | 218 |     |      |
| 7693   | 219 | 233 | 247  |
| MEAN   | 210 | 226 | 235  |
| S.D.   | 8.5 | 5.3 | 14.2 |
| N      | 5   | 4   | 4    |

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SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

FEMALE GROUP: 250 MG/KG

| DAY    | 1   | 8 | 15 |
|--------|-----|---|----|
| ANIMAL |     |   |    |
| 7672   | 204 |   |    |
| 7677   | 186 |   |    |
| 7679   | 192 |   |    |
| 7681   | 195 |   |    |
| 7690   | 193 |   |    |
| MEAN   | 194 |   |    |
| S.D.   | 6.5 |   |    |
| N      | 5   |   |    |

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**APPENDIX VI**

**INDIVIDUAL GROSS NECROPSY OBSERVATIONS  
(LD50 STUDY)**

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL GROSS PATHOLOGY OBSERVATIONS  
(FOUND DEAD)

GRADE

|            |      |                 |           |      |  |        |
|------------|------|-----------------|-----------|------|--|--------|
| ANIMAL NO. | 7657 | GROUP:          | 300 MG/KG | MALE | GROSS: MENINGEAL VESSELS - CONGESTED<br>GROSS: DARK RED FOCI | P<br>P |
|            |      | BRAIN           |           |      | MULTIPLE, ON GLANDULAR MUCOSA                                | P      |
|            |      | STOMACH         |           |      | EXT. APPEARANCE DRIED RED MATERIAL AROUND NOSE               | P      |
| ANIMAL NO. | 7663 | GROUP:          | 300 MG/KG | MALE | GROSS: DARK GREEN MUCOID CONTENTS                            | P      |
|            |      | SMALL INTESTINE |           |      | JEJUNUM  | P      |
|            |      | BRAIN           |           |      | GROSS: MENINGEAL VESSELS - CONGESTED                         | P      |
|            |      | STOMACH         |           |      | GROSS: DARK RED FOCI   | P      |
|            |      | STOMACH         |           |      | MULTIPLE, ON GLANDULAR MUCOSA                                | P      |
|            |      | THYMUS          |           |      | GROSS: REDDISH-BROWN FLUID CONTENTS                          | P      |
|            |      | EXT. APPEARANCE |           |      | GROSS: HEMORRHAGIC   | P      |
|            |      | EXT. APPEARANCE |           |      | GROSS: DRIED RED MATERIAL AROUND EYES                        | P      |
|            |      | EXT. APPEARANCE |           |      | BILATERAL  | P      |
|            |      | EXT. APPEARANCE |           |      | GROSS: DRIED RED MATERIAL AROUND NOSE                        | P      |
|            |      | EXT. APPEARANCE |           |      | GROSS: DRIED LIGHT RED MATTING AROUND MOUTH                  | P      |
| ANIMAL NO. | 7655 | GROUP:          | 350 MG/KG | MALE | GROSS: MENINGEAL VESSELS - CONGESTED                         | P      |
|            |      | BRAIN           |           |      | GROSS: MOTTLED   | P      |
|            |      | LUNGS           |           |      | DARK RED, TAN AND BRIGHT RED, ALL LOBES                      | P      |
|            |      | EXT. APPEARANCE |           |      | GROSS: DRIED RED MATERIAL AROUND MOUTH                       | P      |
|            |      | EXT. APPEARANCE |           |      | GROSS: DRIED RED MATERIAL AROUND NOSE                        | P      |
|            |      | EXT. APPEARANCE |           |      | GROSS: URINE STAIN   | P      |
|            |      | LUNGS           |           |      | UROGENITAL AREA  | P      |
| ANIMAL NO. | 7658 | GROUP:          | 350 MG/KG | MALE | GROSS: DARK GREEN MUCOID CONTENTS                            | P      |
|            |      | SMALL INTESTINE |           |      | JEJUNUM  | P      |
|            |      | LUNGS           |           |      | GROSS: MOTTLED   | P      |
|            |      |                 |           |      | DARK RED AND RED, ALL LOBES                                  | P      |

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SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL GROSS PATHOLOGY OBSERVATIONS  
(FOUND DEAD)

GRADE

| ANIMAL NO. | 7658 (CONT'D) | GROUP: | 350 MG/KG | SEX: | STOMACH         | GROSS: | DARK RED FOCI<br>MULTIPLE, ON GLANDULAR MUCOSA | P |
|------------|---------------|--------|-----------|------|-----------------|--------|--|---|
|            |               |        |           |      | THYMUS          | GROSS: | HEMORRHAGIC<br>ON EXTERNAL AND CUT SURFACES    | P |
|            |               |        |           |      | EXT. APPEARANCE | GROSS: | DRIED RED MATERIAL AROUND NOSE                 | P |
|            |               |        |           |      | EXT. APPEARANCE | GROSS: | URINE STAIN<br>UROGENITAL AREA                 | P |
|            |               |        |           |      |                 |        |  |   |
| ANIMAL NO. | 7659          | GROUP: | 350 MG/KG | SEX: | MALE            | GROSS: | MENINGEAL VESSELS - CONGESTED                  | P |
|            |               |        |           |      | BRAIN           | GROSS: | MOTTLED  | P |
|            |               |        |           |      | LUNGS           | GROSS: | DARK RED AND TAN, ALL LOBES                    | P |
|            |               |        |           |      | STOMACH         | GROSS: | DARK RED FOCI                                  | P |
|            |               |        |           |      |                 | GROSS: | MULTIPLE, ON GLANDULAR MUCOSA                  | P |
|            |               |        |           |      | EXT. APPEARANCE | GROSS: | DRIED RED MATERIAL AROUND NOSE                 | P |
|            |               |        |           |      | EXT. APPEARANCE | GROSS: | DRIED RED MATERIAL AROUND MOUTH                | P |
|            |               |        |           |      |                 |        |  |   |
| ANIMAL NO. | 7667          | GROUP: | 350 MG/KG | SEX: | MALE            | GROSS: | DARK GREEN MUCOID CONTENTS<br>JEJUNUM          | P |
|            |               |        |           |      | SMALL INTESTINE | GROSS: | MENINGEAL VESSELS - CONGESTED                  | P |
|            |               |        |           |      | BRAIN           | GROSS: | DARK RED FOCI                                  | P |
|            |               |        |           |      | STOMACH         | GROSS: | MULTIPLE, ON GLANDULAR MUCOSA                  | P |
|            |               |        |           |      | THYMUS          | GROSS: | HEMORRHAGIC                                    | P |
|            |               |        |           |      | EXT. APPEARANCE | GROSS: | ON EXTERNAL AND CUT SURFACES<br>BILATERAL      | P |
|            |               |        |           |      | EXT. APPEARANCE | GROSS: | DRIED RED MATERIAL AROUND EYES                 | P |
|            |               |        |           |      | EXT. APPEARANCE | GROSS: | DRIED RED MATERIAL AROUND NOSE                 | P |
|            |               |        |           |      | EXT. APPEARANCE | GROSS: | DRIED CLEAR MATTING AROUND MOUTH               | P |
|            |               |        |           |      | EXT. APPEARANCE | GROSS: | URINE STAIN<br>UROGENITAL AREA                 | P |

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL GROSS PATHOLOGY OBSERVATIONS  
(FOUND DEAD)

GRADE

|            |      |        |           |        |                 |   |   |
|------------|------|--------|-----------|--------|-----------------|---|---|
| ANIMAL NO. | 7672 | GROUP: | 250 MG/KG | FEMALE | STOMACH         | GROSS: DARK RED FOCI<br>MULTIPLE, ON GLANDULAR MUCOSA                   | P |
|            |      |        |           |        | STOMACH         | GROSS: DARK BROWN MUCOID CONTENTS                                       | P |
|            |      |        |           |        | THYMUS          | GROSS: HEMORRHAGIC  | P |
|            |      |        |           |        |                 | ON EXTERNAL AND CUT SURFACES  | P |
|            |      |        |           |        | EXT. APPEARANCE | GROSS: DRIED RED MATERIAL AROUND EYES<br>BILATERAL                      | P |
|            |      |        |           |        | EXT. APPEARANCE | GROSS: DRIED RED MATERIAL AROUND NOSE                                   | P |
|            |      |        |           |        | EXT. APPEARANCE | GROSS: DRIED LIGHT RED MATTING AROUND MOUTH                             | P |
| ANIMAL NO. | 7677 | GROUP: | 250 MG/KG | FEMALE | SMALL INTESTINE | GROSS: DARK GREEN MUCOID CONTENTS<br>JEJUNUM                            | P |
|            |      |        |           |        | STOMACH         | GROSS: DARK RED FOCI<br>MULTIPLE, LINEAR AND FOCAL, ON GLANDULAR MUCOSA | P |
|            |      |        |           |        | EXT. APPEARANCE | GROSS: DRIED RED MATERIAL AROUND NOSE                                   | P |
| ANIMAL NO. | 7679 | GROUP: | 250 MG/KG | FEMALE | SMALL INTESTINE | GROSS: DARK GREEN MUCOID CONTENTS<br>JEJUNUM                            | P |
|            |      |        |           |        | STOMACH         | GROSS: DARK RED FOCI<br>MULTIPLE, LINEAR AND FOCAL, ON GLANDULAR MUCOSA | P |
|            |      |        |           |        | EXT. APPEARANCE | GROSS: DRIED CLEAR MATTING AROUND MOUTH                                 | P |
| ANIMAL NO. | 7681 | GROUP: | 250 MG/KG | FEMALE | STOMACH         | GROSS: DARK RED FOCI<br>MULTIPLE, ON GLANDULAR MUCOSA                   | P |
|            |      |        |           |        | EXT. APPEARANCE | GROSS: DRIED RED MATERIAL AROUND MOUTH                                  | P |
|            |      |        |           |        | EXT. APPEARANCE | GROSS: DRIED LIGHT RED MATTING AROUND MOUTH                             | P |

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

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SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL GROSS PATHOLOGY OBSERVATIONS  
(FOUND DEAD)

GRADE

|            |      |        |           |                 |   |   |
|------------|------|--------|-----------|-----------------|---|---|
| ANIMAL NO. | 7690 | GROUP: | 250 MG/KG | FEMALE          | GROSS: DARK RED FOCI<br>STOMACH MULTIPLE, ON GLANDULAR MUCOSA | P |
|            |      |        |           | THYMUS          | GROSS: HEMORRHAGIC<br>ON EXTERNAL AND CUT SURFACES            | P |
|            |      |        |           | EXT. APPEARANCE | GROSS: DRIED RED MATERIAL AROUND EYES<br>BILATERAL            | P |
|            |      |        |           | EXT. APPEARANCE | GROSS: DRIED RED MATERIAL AROUND NOSE                         | P |
|            |      |        |           | EXT. APPEARANCE | GROSS: DRIED CLEAR MATTING AROUND MOUTH                       | P |
| ANIMAL NO. | 7683 | GROUP: | 200 MG/KG | FEMALE          | GROSS: DARK RED FOCI<br>STOMACH MULTIPLE, ON GLANDULAR MUCOSA | P |
|            |      |        |           | EXT. APPEARANCE | GROSS: DRIED LIGHT RED MATTING AROUND MOUTH                   | P |
|            |      |        |           | EXT. APPEARANCE | GROSS: DRIED RED MATERIAL AROUND NOSE                         | P |
|            |      |        |           | EXT. APPEARANCE | GROSS: DRIED RED MATERIAL AROUND EYES<br>BILATERAL            | P |

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

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SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL GROSS PATHOLOGY OBSERVATIONS  
(SCHEDULED SACRIFICE)

GRADE

| ANIMAL NO. | GROUP: | 300 MG/KG        | MALE   | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
|------------|--------|------------------|--------|---|
| ANIMAL NO. | 7660   | GROUP: 300 MG/KG | MALE   | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7671   | GROUP: 300 MG/KG | MALE   | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7649   | GROUP: 250 MG/KG | MALE   | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7653   | GROUP: 250 MG/KG | MALE   | GROSS: HAIRLOSS<br>EXT. APPEARANCE<br>RIGHT AND LEFT FORELIMBS AND RIGHT HINDLIMB |
| ANIMAL NO. | 7661   | GROUP: 250 MG/KG | MALE   | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7666   | GROUP: 250 MG/KG | MALE   | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7669   | GROUP: 250 MG/KG | MALE   | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7652   | GROUP: 350 MG/KG | MALE   | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7675   | GROUP: 150 MG/KG | FEMALE | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7682   | GROUP: 150 MG/KG | FEMALE | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7686   | GROUP: 150 MG/KG | FEMALE | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7687   | GROUP: 150 MG/KG | FEMALE | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |
| ANIMAL NO. | 7695   | GROUP: 150 MG/KG | FEMALE | GROSS: NO SIGNIFICANT CHANGES OBSERVED  |

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

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SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
INDIVIDUAL GROSS PATHOLOGY OBSERVATIONS  
(SCHEDULED SACRIFICE)

GRADE

| ANIMAL NO. | GROUP: | 200 MG/KG        | FEMALE | GROSS: NO SIGNIFICANT CHANGES OBSERVED |
|------------|--------|------------------|--------|--|
| ANIMAL NO. | 7676   | GROUP: 200 MG/KG | FEMALE | GROSS: NO SIGNIFICANT CHANGES OBSERVED |
| ANIMAL NO. | 7678   | GROUP: 200 MG/KG | FEMALE | GROSS: NO SIGNIFICANT CHANGES OBSERVED |
| ANIMAL NO. | 7693   | GROUP: 200 MG/KG | FEMALE | GROSS: NO SIGNIFICANT CHANGES OBSERVED |

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

**APPENDIX VII**

**LD50 CALCULATIONS**

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
PROBIT ANALYSIS (LITCHFIELD-WILCOXON APPROXIMATION)

| DOSEAGE | DIED/<br>TESTED | %<br>OBSERVED | MALE                 |                       |
|---------|-----------------|---------------|----------------------|-----------------------|
|         |                 |               | %<br>EXPECTED        | OBSERVED-<br>EXPECTED |
| 250.0   | 0/ 5            | 0.0           | 1.9                  | 1.9                   |
| 300.0   | 2/ 5            | 40.0          | 33.6                 | 6.4                   |
| 350.0   | 4/ 5            | 80.0          | 83.2                 | 3.2                   |
|         |                 |               | TOTAL CONTRIBUTION = | 0.046                 |

ACTUAL CHI = 0.23, TABLE CHI = 3.84; THEREFORE DATA ARE NOT SIGNIFICANTLY HETEROGENEOUS

TOTAL ANIMALS = 15

K = NO. OF DOSES PLOTTED = 3

ANIMALS/DOSE = 5

N = K-2 = 1 (DEGREES OF FREEDOM)

LD90 = 358.

LD50 = 315.

LD10 = 276. S = 1.12

N' = 10 (TOTAL NUMBER OF ANIMALS BETWEEN 16% AND 84% EXPECTED EFFECTS)

SQRT(N') = 3.16

FLD50 = 1.10

LD50 AND THE 95% CONFIDENCE LIMITS ARE 315. ( 285. - 347. )

R = LARGEST/SMALLEST DOSE = 1.40

A = 1.04

FS = 1.09

SLOPE AND THE 95% CONFIDENCE LIMITS ARE 1.12 ( 1.03 - 1.22 )

**PUBLIC NOTICE COPY**

SLS STUDY NO.: 3147 45                    ACUTE ORAL TOXICITY STUDY IN RATS  
CLIENT: RHONE-POULENC AG COMPANY       PROBIT ANALYSIS (LITCHFIELD-WILCOXON APPROXIMATION)

| MALE   |                 |                                 |                    |
|--------|-----------------|---------------------------------|--------------------|
| DOSAGE | DIED/<br>TESTED | LD50 WITH 95% CONFIDENCE LIMITS |                    |
|        |                 | MORTALITY                       | AND SLOPE FUNCTION |
| 250.0  | 0/ 5            | 0.0%                            | LD50 - 315.        |
| 300.0  | 2/ 5            | 40.0%                           | ( 285. - 347. )    |
| 350.0  | 4/ 5            | 80.0%                           |                    |

SLS STUDY NO.: 3147 45  
CLIENT: RHONE-POULENC AG COMPANY

ACUTE ORAL TOXICITY STUDY IN RATS  
PROBIT ANALYSIS (LITCHFIELD-WILCOXON APPROXIMATION)

| F E M A L E |                 |               |               |                       |                          |
|-------------|-----------------|---------------|---------------|-----------------------|--------------------------|
| DOSAGE      | DIED/<br>TESTED | %<br>OBSERVED | %<br>EXPECTED | OBSERVED-<br>EXPECTED | CONTRIBUTION<br>TO (CHI) |
| 150.0       | 0/ 5            | 0.0           | 0.0           | 0.0                   | 0.000                    |
| 200.0       | 1/ 5            | 20.0          | 20.0          | 0.0                   | 0.000                    |
| 250.0       | 5/ 5            | 100.0         | 100.0         | 0.0                   | 0.000                    |
|             |                 |               |               | TOTAL CONTRIBUTION =  | 0.000                    |

ACTUAL CHI = 0.00, TABLE CHI = 3.84; THEREFORE DATA ARE NOT SIGNIFICANTLY HETEROGENEOUS

TOTAL ANIMALS = 15  
K = NO. OF DOSES PLOTTED = 3  
ANIMALS/DOSE = 5  
N = K-2 = 1 (DEGREES OF FREEDOM)

LD90 = 219.  
LD50 = 208.  
LD10 = 197.  
S = 1.05

N' = 5 (TOTAL NUMBER OF ANIMALS BETWEEN 16% AND 84% EXPECTED EFFECTS)  
 $\text{SQRT}(N') = 2.24$   
 $\text{FLD50} = 1.06$

LD50 AND THE 95% CONFIDENCE LIMITS ARE 208. ( 196. - 220.)

R = LARGEST/SMALLEST DOSE = 1.67  
A = 1.00  
FS = 1.01

SLOPE AND THE 95% CONFIDENCE LIMITS ARE 1.05 ( 1.03 - 1.06)

**PUBLIC NOTICE COPY.**

|        |                 | F E M A L E   |   |              |        |      |
|--------|-----------------|---|---|--------------|--------|------|
|        |                 | LD50 WITH 95% CONFIDENCE LIMITS<br>AND SLOPE FUNCTION |   |              |        |      |
| DOSAGE | DIED/<br>TESTED | MORTALITY   |   |              | LD50 - | 208. |
| 150.0  | 0/ 5            | 0.0%  |   |              |        |      |
| 200.0  | 1/ 5            | 20.0%   |   |              |        |      |
| 250.0  | 5/ 5            | 100.0%  |   |              |        |      |
|        |                 |   | ( | 196. - 220.) |        |      |

CAP ID No:  
Balsamroot Ssp. 8 (e)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

Glenn S. Simon, Ph.D., DABT  
Director of Toxicology  
Rhône-Poulenc  
P.O. Box 12014  
2 T.W. Alexander Drive  
Research Triangle Park, North Carolina 27709

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MAR 30 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)  
Attn: TSCA Section 8(e) Coordinator  
Office of Pollution Prevention and Toxics  
U.S. Environmental Protection Agency  
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan  
Terry R. O'Bryan  
Risk Analysis Branch

Enclosure

12185A



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## Triage of 8(e) Submissions

Date sent to triage: MAY 10 1995

NON-CAP

CAP

Submission number: 12185A

TSCA Inventory:

Y

N

D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN

w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): \_\_\_\_\_

Notes:

**THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY**

For Contractor Use Only

entire document

0

1

2

pages

123

pages 123, TAB

Notes:

Contractor reviewer:

PJR

Date:

5/22/95

## C:CATS/STRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: 1192 - 12185 SEQ. A  
Submission #: SEHQ-A

TYPE: INT. SUPP FLWTP

SUBMITTER NAME: Rhone - Poulenec Inc.

INFORMATION REQUESTED: FLWTP DATE:

- 0501 NO INFO REQUESTED
- 0502 INFO REQUESTED (TECH)
- 0503 INFO REQUESTED (VOL ACTIONS)
- 0504 INFO REQUESTED (REPORTING RATIONALE)
- 0505 REFER TO CHEMICAL SCREENING
- 0506 CAP NOTICE
- 0507 PRODUCTION DISCONTINUED
- 0508 CONFIDENTIAL

SUB. DATE: 10/27/92 OTS DATE: 10/02/92 CSRAD DATE: 02/08/95

CHEMICAL NAME:  
Anilinate

RPA: 909446

VOLUNTARY ACTIONS:

- 0401 NO ACTION REQUESTED
- 0402 STUDIES/PLANNING/INDUSTRY
- 0403 NOTIFICATION ON WORKING CONDITIONS
- 0404 LABELING/CLARIFICATIONS
- 0405 PROCESS/HANDLING/CHANGES
- 0406 APP/USE DISCONTINUED
- 0407 PRODUCTION DISCONTINUED
- 0408 CONFIDENTIAL

P.F.C.INFORMATION TYPE:

- |   |   |
|---|---|
| <input type="checkbox"/> 0216 EPICLIN                   | <input type="checkbox"/> 0241 IMMUNO (ANIMAL)           |
| <input type="checkbox"/> 0217 HUMAN EXPOS (PROD CONTAM) | <input type="checkbox"/> 0242 IMMUNO (HUMAN)            |
| <input type="checkbox"/> 0218 HUMAN EXPOS (ACCIDENTAL)  | <input checked="" type="checkbox"/> 0243 CHIEMPHYS PROP |
| <input type="checkbox"/> 0219 HUMAN EXPOS (MONITORING)  | <input type="checkbox"/> 0244 CLASTO (IN VITRO)         |
| <input type="checkbox"/> 0220 ECOLAQ/AQUA TOX           | <input type="checkbox"/> 0245 CLASTO (ANIMAL)           |
| <input type="checkbox"/> 0221 ENV. OCCUREL/FATE         | <input type="checkbox"/> 0246 CLASTO (HUMAN)            |
| <input type="checkbox"/> 0222 EMER INCI OF ENV CONTAM   | <input type="checkbox"/> 0247 DNA DAM/REPAIR            |
| <input type="checkbox"/> 0223 RESPONSE REQUEST DELAY    | <input checked="" type="checkbox"/> 0248 PRODUCE/PROC   |
| <input type="checkbox"/> 0224 PROD/COMP/CHM ID          | <input type="checkbox"/> 0251 MSDS                      |
| <input type="checkbox"/> 0225 REPORTING RATIONALE       | <input type="checkbox"/> 0259 OTHER                     |

INFORMATION TYPE:

- |   |   |
|---|---|
| <input type="checkbox"/> 0101 ONCO (HUMAN)              | <input type="checkbox"/> 0216 EPICLIN                   |
| <input type="checkbox"/> 0202 ONCO (ANIMAL)             | <input type="checkbox"/> 0217 HUMAN EXPOS (PROD CONTAM) |
| <input type="checkbox"/> 0203 CELL. TRANS (IN VITRO)    | <input type="checkbox"/> 0218 HUMAN EXPOS (ACCIDENTAL)  |
| <input type="checkbox"/> 0204 MUTA (IN VITRO)           | <input type="checkbox"/> 0219 HUMAN EXPOS (MONITORING)  |
| <input type="checkbox"/> 0205 MUTA (IN VIVO)            | <input type="checkbox"/> 0220 ECOLAQ/AQUA TOX           |
| <input type="checkbox"/> 0206 REPRO/TERATO (HUMAN)      | <input type="checkbox"/> 0221 ENV. OCCUREL/FATE         |
| <input type="checkbox"/> 0207 REPRO/TERATO (ANIMAL)     | <input type="checkbox"/> 0222 EMER INCI OF ENV CONTAM   |
| <input type="checkbox"/> 0208 NEURO (HUMAN)             | <input type="checkbox"/> 0223 RESPONSE REQUEST DELAY    |
| <input checked="" type="checkbox"/> 0209 NEURO (ANIMAL) | <input type="checkbox"/> 0224 PROD/COMP/CHM ID          |
| <input type="checkbox"/> 0210 ACUTE TOX. (HUMAN)        | <input type="checkbox"/> 0225 REPORTING RATIONALE       |
| <input type="checkbox"/> 0211 CHR. TOX. (HUMAN)         | <input type="checkbox"/> 0226 CONFIDENTIAL              |
| <input type="checkbox"/> 0212 ACUTE TOX. (ANIMAL)       | <input type="checkbox"/> 0227 ALLERG (HUMAN)            |
| <input type="checkbox"/> 0213 SUB ACUTE TOX (ANIMAL)    | <input type="checkbox"/> 0228 ALLERG (ANIMAL)           |
| <input type="checkbox"/> 0214 SUB CHRONIC TOX (ANIMAL)  | <input type="checkbox"/> 0229 METAB/PHARMACO (ANIMAL)   |
| <input type="checkbox"/> 0215 CHRONIC TOX (ANIMAL)      | <input type="checkbox"/> 0240 METAB/PHARMACO (HUMAN)    |

P.F.C.INFORMATION TYPE:

- |                                    |   |
|------------------------------------|---|
| <input type="checkbox"/> 0101 RATT | <input type="checkbox"/> 0241 IMMUNO (ANIMAL)           |
| <input type="checkbox"/> 0102 RATT | <input type="checkbox"/> 0242 IMMUNO (HUMAN)            |
| <input type="checkbox"/> 0103 RATT | <input checked="" type="checkbox"/> 0243 CHIEMPHYS PROP |
| <input type="checkbox"/> 0104 RATT | <input type="checkbox"/> 0244 CLASTO (IN VITRO)         |
| <input type="checkbox"/> 0105 RATT | <input type="checkbox"/> 0245 CLASTO (ANIMAL)           |
| <input type="checkbox"/> 0106 RATT | <input type="checkbox"/> 0246 CLASTO (HUMAN)            |
| <input type="checkbox"/> 0107 RATT | <input type="checkbox"/> 0247 DNA DAM/REPAIR            |
| <input type="checkbox"/> 0108 RATT | <input checked="" type="checkbox"/> 0248 PRODUCE/PROC   |
| <input type="checkbox"/> 0109 RATT | <input type="checkbox"/> 0251 MSDS                      |
| <input type="checkbox"/> 0110 RATT | <input type="checkbox"/> 0259 OTHER                     |

USE:

- R.D. Pesticide

TOXICOLOGICAL CONCERN:

- |                              |                               |
|------------------------------|-------------------------------|
| <input type="checkbox"/> LOW | <input type="checkbox"/> MED  |
| <input type="checkbox"/> MED | <input type="checkbox"/> HIGH |

PRODUCTION:

- |                              |   |
|------------------------------|---|
| <input type="checkbox"/> YES | <input type="checkbox"/> NO                 |
| <input type="checkbox"/> NO  | <input checked="" type="checkbox"/> UNKNOWN |

TRIAGE DATE: NON CBL INVENTORY  
CAS SR: NO

ONGOING REVIEW: YES (DROP/REFER)  
NO (CONTINUE): NEVER

DISPOSITION: DISCONTINUED

SEARCHED: SEARCHED - 091 - 12825, 0989 - 0825 S

-CPSS- 0929951235

0 0 0 0 0 0 0 0 0 0 0 0

> <ID NUMBER>

8(e)-12185A

> <TOX CONCERN>

M

> <COMMENT>

ACUTE ORAL TOXICITY IN RATS IS MEDIUM CONCERN WITH MALE AND FEMALE LD50S OF 315 AND 208 MG/KG, RESPECTIVELY. DOSE (MG/KG) AND MORTALITY: 150 (0/5 F), 200 (1/5 F), 250 (0/5 M, 5/5 M), 300 (2/5 M), AND 350 (4/5 M). CLINICAL SIGNS INCLUDED APPARENT FORELIMB PARALYSIS, DECREASED ACTIVITY, ATAXIA, LABORED BREATHING, URINE STAINS AND DARK MATERIAL ON FACIAL AREA, SALIVATION, AND HAIR LOSS. NECROPSY IN DECEDENTS REVEALED DARK RED FOCI ON STOMACH, MOTTLED LUNGS, HEMORRHAGIC THYMUS AND CONGESTED MENINGEAL VESSELS OF THE BRAIN. NO REMARKABLE CHANGES WERE NOTED IN SURVIVORS. IN A RANGE- FINDING STUDY, 2 ANIMALS WERE TREATED PER DOSE (1/SEX). THE RESULTS WERE 100 (0/2), 200 (0/2), 300 (2/2), 500 (2/2) AND 1000 (2/2).

\$\$\$\$





TOXICOLOGY DEPARTMENT  
P.O. BOX 12014, 2 T.W. ALEXANDER DRIVE  
RESEARCH TRIANGLE PARK, N.C. 27709  
(919) 549-2000 TELEFAX (919) 549-2925  
INTERNATIONAL TELEX NUMBER 4999378 - ANSWERBACK APC RTP

8E CAP f/w P  
Contains No CB

Contains No CB

June 16, 1993

B

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8EHQ-92-12185  
SP001  
09930000203

Document Processing Center (TS-790)  
(ATTN: Section 8(e) Coordinator)  
Office of Toxic Substances  
US Environmental Protection Agency  
401 M Street, SW  
Washington, DC 20460

RE: TSCA Section 8(e) Notices on: Anilate (CAP)

Dear Sir or Madam:

Via this letter, Rhône-Poulenc Ag Company relinquishes our claims of confidentiality made for TSCA Section 8(e) submissions on RPA 90946 (CAS number 113136-77-9 and CAS name 1-[[[2,4-dichlorophenyl]amino]carbonyl]cyclopropanecarboxylic acid). Six separate submissions dated October 27, 1992 were made on this chemical under the Compliance Audit Program (CAP ID Number 8ECAP-0004). To our knowledge, EPA Document Control Numbers have not yet been assigned to these submissions. In addition, three "NON-CAP" submissions have been made on this chemical. Two of these submissions are identified by the EPA Document Control Numbers of 8EHQ-0791-1282S and 8EHQ-0792-5229S. The third submission was submitted on October 7, 1992, but we have not yet received the EPA Document Control Number for this submission.

Further questions regarding this letter may be directed to the undersigned at 919-549-2222.

Sincerely,

Glenn S. Simon, PhD, DABT  
Director of Toxicology

2/23/95